Original Article

Recurrent Acute Rhinosinusitis Prevention by Azithromycin in Children with Nonallergic Rhinitis

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What is already known about this topic? Recurrent acute rhinosinusitis (RARS) has a considerable impact on quality of life and impairment of daily function. Role of antibiotics to prevent RARS in children with nonallergic rhinitis (NAR) has not been investigated.

What does this article add to our knowledge? Azithromycin prophylaxis can reduce the number of rhinosinusitis episodes and medication score, and improve nasal symptoms in NAR children with RARS. The number needed to treat using azithromycin prophylaxis to prevent 1 patient from having RARS was 2.

How does this study impact current management guidelines? These data support the efficacy of azithromycin prophylaxis to prevent RARS in children with NAR.

BACKGROUND: Recurrent acute rhinosinusitis (RARS) is characterized by multiple episodes of acute rhinosinusitis between which symptoms and signs resolve completely. The role of antibiotic prophylaxis to prevent RARS in children with nonallergic rhinitis (NAR) has not been investigated.
OBJECTIVE: To evaluate the effect of azithromycin to prevent RARS in children with NAR.
METHODS: A randomized, double-blind, placebo-controlled study was conducted in NAR children (5-15 years) with RARS. Azithromycin (5 mg/kg/d) 3 d/wk for 12 months or placebo was assigned to the study group and the control group, respectively. Patients with allergic rhinitis were excluded. Number of rhinosinusitis episodes in 12 months, visual analog scale score of nasal symptoms, and adjunctive medication score were recorded.
RESULTS: Forty patients were enrolled and 20 patients were assigned randomly to the azithromycin and placebo groups. IgG subclass and specific antibody deficiencies were found in 83% and 2.5% of patients, respectively. After 12 months, the number of rhinosinusitis episodes/y in the azithromycin group reduced significantly from 5 to 0.5 ($P < .001$) in contrast to the placebo group. Number needed to treat using azithromycin prophylaxis to prevent 1 patient from having RARS was 2. The average visual analog scale score and the average adjunctive medication score in the azithromycin (but not in the placebo) group reduced significantly compared with baseline (2.2 ± 1.4 vs 5.4 ± 1.8) and (3.9 ± 1.7 vs 5.4 ± 1.1), respectively ($P < .001$).
CONCLUSIONS: Azithromycin prophylaxis can reduce the number of rhinosinusitis episodes and medication score, and improve nasal symptoms in NAR children with RARS. © 2017 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2017;■:■-■)

Key words: *Azithromycin; Children; Nonallergic rhinitis; Recurrent acute rhinosinusitis; Rhinitis; Sinusitis; Prevention*

Pediatric rhinosinusitis is a common medical problem. In children, it is estimated that 5% to 10% of upper respiratory tract infections (URIs) are complicated by acute rhinosinusitis (ARS) and that 6% to 13% of all children develop rhinosinusitis by the age of 3 years.[1] Early recognition and adequate management are the main strategies to improve outcome. Pediatric rhinosinusitis is categorized as acute, subacute, or chronic. ARS lasts 10 to 30 days, subacute rhinosinusitis lasts 4 to 12 weeks, and chronic rhinosinusitis (CRS) lasts more than 12 weeks.[2] Recurrent acute rhinosinusitis (RARS) is characterized by multiple episodes of ARS where the symptoms and signs of infection resolve completely between episodes.[3,4] RARS and CRS have been found in 11.5% and 18.9% of cases of pediatric rhinosinusitis, respectively.[5] Children with CRS or RARS need a prolonged course of antibiotics and frequent health care utilization. These conditions have a considerable impact on quality of life and impairment of daily function.[6-8]

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Abbreviations used
AMS- adjunctive medication score
AR- allergic rhinitis
ARS- acute rhinosinusitis
CF- cystic fibrosis
CRS- chronic rhinosinusitis
NAR- nonallergic rhinitis
RARS- recurrent acute rhinosinusitis
URI- upper respiratory tract infection
VAS- visual analog scale

RARS and CRS are uncommon conditions in healthy children. Hence, children should be evaluated for underlying diseases such as allergic rhinitis (AR) and nonallergic rhinitis (NAR), immunodeficiency, ciliary dysfunction, gastroesophageal reflux, and anatomical abnormalities of the osteomeatal complex (including septal deviation, nasal polyps, and concha bullosa).[5,9-11] Several strategies have been suggested to prevent RARS: adequate duration of antibiotics; saline irrigation; avoidance of exposure to smoke; reduced attendance at daycare centers; vaccines against influenza and *Haemophilus influenzae* type b; removal of adenoids; and treatment of underlying factors (eg, AR, gastroesophageal reflux, and anatomical obstruction).[11-14] A prolonged course of antibiotics in CRS has been associated with beneficial outcome in several reports.[15,16]

A prospective randomized controlled trial to determine the efficacy of prophylactic antibiotics for RARS in children is lacking. The objective of the present study was to evaluate the effect of azithromycin to prevent RARS in children with NAR. Patients with AR were excluded because the most specific therapy for moderate-to-severe AR is allergen immunotherapy.

METHODS

Study design

This was a 12-month prospective, randomized, double-blind, placebo-controlled study (Figure 1). The study protocol was approved by the Institutional Review Board of Siriraj Hospital (Mahidol University, Bangkok, Thailand; approval code: 394/2551(EC4)). Written informed consent was obtained from the parents/guardians of each child.

Participants

Children aged 5 to 15 years diagnosed as having RARS in pediatric allergy clinic and otorhinolaryngology clinic at Siriraj Hospital were recruited. The number of rhinosinusitis episodes was determined from medical records. *ARS* was defined as persistent symptoms of a URI lasting more than 10 days but less than 30 days, or worsening symptoms of a URI after initial improvement, or severe symptoms at onset (purulent nasal discharge for 3-4 days with high fever).[3,4,17] *RARS* was defined as 3 episodes of ARS in 6 months or 4 episodes in 12 months, each lasting less than 30 days and separated by intervals of 10 days or more during which the patient was asymptomatic.[3,4] Patients who had CRS (symptoms of rhinosinusitis lasting more than 90 days and asymptomatic less than 10 days between episodes of rhinosinusitis),[3,4] AR, a history of allergic reactions to azithromycin or macrolides, or underlying diseases (eg, chronic renal diseases, liver diseases, or cardiovascular diseases) were excluded from this study, as were patients who received other preventive therapy (eg, nasal irrigation with gentamicin or intravenous immunoglobulin).

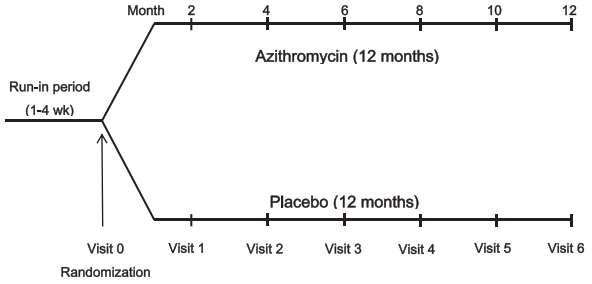

FIGURE 1. Overview of the study design.

Interventions

Patients in the "active" group received azithromycin oral suspension (5 mg/kg body weight/d; Zithromax; Pfizer, New York, NY) on 3 nonconsecutive days per week (eg, Monday, Wednesday, and Friday) for 12 months. A placebo was prepared by a pharmacist (T.T.), and was identical to the oral suspension of azithromycin in appearance, texture, smell, taste, labeling, and packaging. Before administration, the oral powder of the trial medication was reconstituted with 9 mL of water in a bottle to give a total volume of 15 mL per bottle. The viscosity of the placebo was identical to that of azithromycin after reconstitution. A 12-month period was designed to overcome the seasonal variation of URI. Patients were asked to return the bottle at each visit to ensure compliance.

All patients were instructed to use normal saline nasal irrigation. They were allowed to use adjunctive medications for relief of rhinitis symptoms if needed (eg, intranasal corticosteroids, oral antihistamines, oral leukotriene receptor antagonists, and oral decongestants). Patients and their parents were instructed to keep a diary during the study period, for a daily evaluation of nasal symptoms and adjunctive medications.

During the study period, all patients were instructed to come to the pediatric allergy clinic or pediatric outpatient clinic for any illness and they were evaluated by J.V. The patients who had ARS, defined by the American Academy of Pediatrics criteria,[3,4] were documented and treated with antibiotic therapy (excluded azithromycin) for 10 to 14 days. The azithromycin prophylaxis was stopped during that period and restarted after the treatment of ARS.

Randomization

Block-of-four randomization was used for allocation sequencing of patients using numbered containers. T.T. and O.J. generated the allocation sequence and assigned patients to their groups. J.V. enrolled patients and assessed outcomes. J.V. and patients were blinded to group assignment from the beginning of assignment to the end of interventions. Interventions were decoded at the end of the study by O.J.

Procedures

In the run-in period, all children were evaluated for allergic sensitization and immune function. Serum IgG, IgA, IgM as well as IgG subclass and antibody responses to pneumococcal immunization were assessed. The skin prick test was done with a panel of the most prevalent local aeroallergens: house dust mites (*Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*); American and German cockroaches; dander from cats and dogs; grass pollens (Bermuda, Johnson); Acacia; and careless weeds and molds (*Alternaria* spp, *Cladosporium* spp, *Penicillium* spp, *Aspergillus* spp, and *Fusarium* spp). Commercial allergens from ALK-Abello (Port